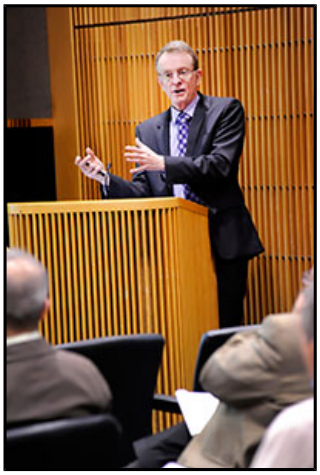
New approaches in mustard gas exposure treatment

By Monica Frazier

As part of the Keystone Science Lecture Seminar Series, highlighting the broad range of research by its grantees, NIEHS hosted a talk Feb. 6 by pediatric pulmonologist Carl White, M.D. His current research, funded by the NIH Countermeasures Against Chemical Threats (CounterACT) *(http://www.ninds.nih.gov/research/counterterrorism/counterACT_home.htm)* program, focuses on the prevention and treatment of respiratory damage from exposure to the toxic vesicants, or blistering agents, sulfur, nitrogen, mustards, and chlorine gas.



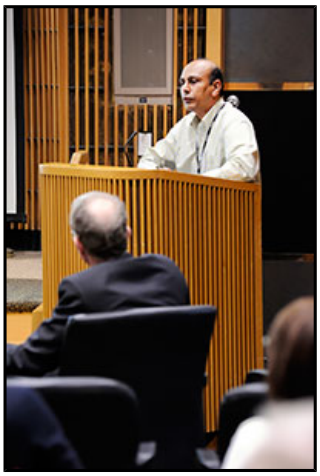
White described his research group's progress in the treatment of mustard-gas exposed rodents to a group of NIEHS and NTP researchers, many of them from the Laboratory of Respiratory Biology. (Photo courtesy of Steve McCaw)

The presentation, "Novel Countermeasures Against Chemically Induced Airways Injury," outlined the progress White's group has made toward mustard gas post-exposure therapeutics. According to White, mustard gas was one of the deadliest chemical agents used in World War I, and still poses a chemical threat to public health through accidental spill, terrorist attack, or use by military forces in countries such as Libya and Syria, which still have significant stockpiles.

White is a professor of pediatrics and director of the Pediatric Airway Research Center, as well as director of the CounterACT Center of Excellence *(http://www.nationaljewish.org/counteract/overview)* at the University of Colorado (UC) Denver.

The continuing threat of mustard gas

Although sometimes thought of as a weapon that is out of date, mustard gas maintains a presence in many countries for use as a chemical weapon. as well as in depots for eventual disposal, such as ones in Pueblo, Colo., and elsewhere.



Nadadur hosted White's talk, introducing White and monitoring the question-and-answer session that followed. (Photo courtesy of Steve McCaw)

NIH CounterACT funding promotes the development of countermeasures against chemical warfare threats, such as mustard gas. Surprisingly, even nearly a century after development of mustard gas, the best treatment for exposure has not been definitively determined, which is exactly what White aims to do.

White detailed his research program during the lecture, saying, "[Its goals are] to develop or optimize anticoagulants, fibrinolytics, and catalytic antioxidants to rescue or prevent airway injury or death due to vesicants."

As Sri Nadadur, Ph.D., program director overseeing the CounterACT program at NIEHS, explained in his introduction, "The research effort on the use of fibrinolytics as a countermeasure for sulfur mustard-induced pulmonary injury is promising and going in the right direction."

Effective post-exposure treatments with FDA approved drugs

Airway occlusions, a type of blockage of normal respiration, are often seen in mustard gas-exposed patients as a result of fibrin lesions or casts. White and his colleagues have found some of the same fibrinolytic drugs, already approved by the U.S. Food and Drug Administration (FDA) to treat strokes, myocardial infarction, and other conditions, to be extremely beneficial in rats exposed to mustard gas. For example, treatment post-exposure with tissue plasminogen activator (tPA) shows impressive results, including markedly better oxygen saturation, clinical scores, and survival rates.

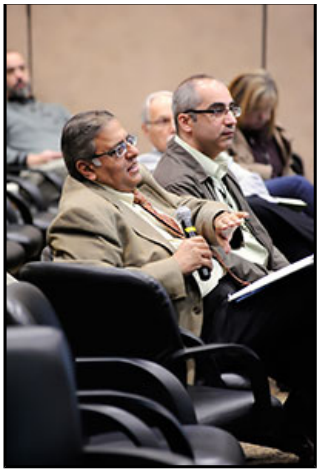
In addition to tPA, tissue factor pathway inhibitor (TFPI) and heparin, which is commonly used in children affected with plastic bronchitis, are also being investigated as therapeutics. In the heparin-treated group, considerable relief of symptoms was seen with treatment every four hours, and full survival at 48 hours, but White made a point that the treatments were started early after exposure.

In addition to their 48-hour studies, White and colleagues are performing 28-day studies with a broad-spectrum catalytic antioxidant, AEOL 10150. "This is the first nonairway administered drug that we've been able to find that has efficacy in the sulfur mustard model," he said.

Despite significant improvement in the treated rodents, survival after 48-72 hours is not yet ideal without continued treatment. In the future, White hopes to move into a second species to test rescue drugs, or quick relief medications, so that his group can begin to focus on how to manage treatment with chronic disease in surviving patients.

Future studies at UC Denver and the U.S. Army Research Laboratory at the Aberdeen Proving Ground in Maryland, will explore the health effects of lower doses of mustard gas, and develop models for mustard gas inhalation to test effects of chlorine gas exposure.

(Monica Frazier, Ph.D., is an Intramural Research Training Award fellow in the NIEHS Mechanisms of Mutation Group.)



University of Texas Southwestern Medical Center clinical researcher Rashmin Savani, M.D., left, was on hand as a guest of Stavros Garantziotis, M.D., right, acting director of the NIEHS Clinical Research Program and NIEHS Clinical Research Unit Medical Director. (Photo courtesy of Steve McCaw)

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